

466224 PMID: 15505412

Apoptosome dysfunction in human cancer.

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Apoptosis - an international journal on programmed cell death (United States) Nov 2004, 9 (6) p691-704, ISSN 1360-8185 Journal Code: 9712129

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Apoptosis is a cell suicide mechanism that enables organisms to control cell number and eliminate cells that threaten survival. The apoptotic cascade can be triggered through two major pathways. Extracellular signals such as members of the tumor necrosis factor (TNF) family can activate the receptor-mediated extrinsic pathway. Alternatively, stress signals such as DNA damage, hypoxia, and loss of survival signals may trigger the mitochondrial intrinsic pathway. In the latter, mitochondrial damage results in cytochrome c release and formation of the **apoptosome**, a multimeric protein complex containing Apaf-1, cytochrome c, and caspase-9. Once bound to the **apoptosome**, caspase-9 is activated, and subsequently triggers a cascade of effector caspase activation and proteolysis, leading to apoptotic cell death. Recent efforts have led to the identification of multiple factors that modulate **apoptosome** formation and function. Alterations in the expression and/or function of these factors may contribute to the pathogenesis of cancer and resistance of tumor cells to chemotherapy or radiation. In this review we discuss how disruption of normal **apoptosome** formation and function may lead or contribute to tumor development and progression.

6469178 PMID: 15648737

Hypothermia inhibits Fas-mediated apoptosis of primary mouse hepatocytes in culture.

Fu Tao; Blei Andres T; Takamura Noriaki; Lin Tesu; Guo Danding; Li Honglin; O'Gorman Maurice R; Soriano Humberto E

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Cell transplantation (United States) 2004, 13 (6) p667-76, ISSN 0963-6897 Journal Code: 9208854

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Apoptosis occurs during the isolation and even short-term storage and culture of hepatocytes, and in the pathogenesis of liver diseases, such as hepatic failure and hepatitis. Therapeutic hypothermia has beneficial effects in experimental models of fulminant hepatic failure. The mechanisms underlying the potential benefits of mild hypothermia on the liver have not been well investigated. We examined the effects of temperature on soluble Fas ligand-induced apoptosis in freshly isolated mouse hepatocytes. Decreasing the culture temperature from 37 degrees C to 32 degrees C produced significant suppression of Fas-mediated apoptosis in cultured hepatocytes over a 12-h period. This observation was supported by cell morphology, flow cytometry analysis of cellular DNA content, and Annexin V-FITC staining of membrane phosphatidylserine translocation. In hypothermic conditions, Fas-mediated cytochrome c release from mitochondria of hepatocytes and the proximate downstream activation of caspase-9 were suppressed under mild hypothermic conditions. Effector caspase-7 activity was also inhibited at 32 degrees C. In contrast, the activation of initiator caspase-8 and cleavage of Bid were not affected after Fas-ligand stimulation. These findings suggest that mild hypothermia suppresses Fas-mediated apoptosis of liver cells by the partial inhibition of signaling events including mitochondrial damage, cytochrome c release, and subsequent **apoptosome** formation and effector caspase activation.

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DIALOG(R)File 155:MEDLINE(R)

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16466224 PMID: 15505412

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Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Type I and type II reactions in TRAIL-induced apoptosis -- results from dose-response studies.

Rudner Justine; Jendrossek Verena; Lauber Kirsten; Daniel Peter T; Wesselborg Sebastian; Belka Claus

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Oncogene (England) Jan 6 2005, 24 (1) p130-40, ISSN 0950-9232

Journal Code: 8711562

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Death receptor-induced apoptosis is paradigmatically mediated via the recruitment of FADD adapter molecule to the ligand/receptor complex and subsequent activation of caspase-8. However, several observations provided evidence that components of the mitochondrial apoptosis pathway are involved in death receptor-mediated apoptosis. In this regard, caspase-8-mediated activation of Bid induces the release of cytochrome c from the mitochondria, which, in turn, triggers the formation of the **apoptosome** protein complex, resulting in the activation of caspase-9.

Whereas Bax or Bak were shown to be required for the proapoptotic effect of Bid, Bcl-2 was described to interfere with its action. Up to now, contradictory results regarding the role of Bcl-2 in TRAIL-induced apoptosis have been published. In order to study the influence of Bcl-2 on TRAIL-induced cell death more detailed, we utilized a tetracycline-regulated Bcl-2 expression system in Jurkat T cells. After having analysed the dose response for TRAIL-induced activation of caspase-8, -9, -3, breakdown of the mitochondrial membrane potential, and changes in the apoptotic morphology in cells expressing different Bcl-2 levels, we conclude that overexpression of Bcl-2 mediates a partial resistance towards lower doses of TRAIL that can be overcome when higher doses of TRAIL are applied. Thus, the requirement of the mitochondrial pathway for death receptor-induced apoptosis in type II cells should be reconsidered, since the protective effect of Bcl-2 is limited to lower TRAIL doses or early observation time points.

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17272855 PMID: 15523899

Immunocytochemical detection of members of the caspase cascade of apoptosis in high-grade astrocytomas.

Bodey Bela; Bodey Vivian; Siegel Stuart E; Nasir Aejaz; Coppola Domenico; Hakam Ardeshir; Kaiser Hans E

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In vivo (Athens, Greece) (Greece) Sep-Oct 2004, 18 (5) p593-602,

ISSN 0258-851X Journal Code: 8806809

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

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17281804 PMID: 15632278

Caspase-dependent and -independent neuronal death: two distinct pathways
to neuronal injury.

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Neuroscientist - a review journal bringing neurobiology, neurology and
psychiatry (United States) Feb 2005, 11 (1) p50-62, ISSN 1073-8584

Journal Code: 9504819

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Caspases are cysteine proteases that mediate apoptotic death in a variety
of cellular systems, including neurons. Caspases are activated through
extrinsic or intrinsic pathways. The latter is used by most neurons in most
situations. In this pathway, release of mitochondrial cytochrome c into the
cytoplasm induces formation of the **apoptosome**, which leads to the
activation of caspase 9 and subsequently other caspases. Recent data
demonstrate that when caspase activation is inhibited at or downstream of
the **apoptosome**, neurons undergo a delayed, caspase-independent death.
Furthermore, there are instances, most notably following excitotoxic injury
and calcium overload, in which the direct cell death pathway elicited
differs from classical apoptosis. The molecular and biochemical features of
such caspase-independent, nonapoptotic forms of neuronal death are just
beginning to be elucidated, but alterations at the level of the
mitochondria and noncaspase proteases play significant roles. Mitochondrial
alterations in caspase-independent death may include energy depletion,
generation of free radicals, opening of the permeability transition pore,
and release of cytotoxic proteins, such as apoptosis-inducing factor. The
particular mechanisms employed can be context dependent. In disease states,
in which a combination of apoptotic and nonapoptotic death occurs,
therapeutic strategies need to take into account both caspase-dependent and
-independent pathways.

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